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(54) **Process for the preparation of 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-piperidylmethyl)benzamide (flecainide)**

(57) A process for preparing flecainide comprises reacting para-dibromobenzene or para-dihydroxybenzene with a compound of formula CF_3CH_2O-A wherein A is $-SO_2CF_3$ or an alkali metal, acetylating the resulting 1,4-bis(trifluoroethoxy) benzene to give the bis (trifluoroethoxy) acetophenone in the presence of a Lewis acid catalyst, then either chlorinating the acetylated product, adding a buffering base and further chlorinating to form the corresponding α, α, α-trichloroacetophenone or reacting the acetylated acetophenone with hypochlorite to form the corresponding benzoic acid and reacting the acid with an inorganic acid chloride to provide the corresponding acid chloride, and then reacting the product of either of the latter pair of steps with 2-amino-methyl-piperidine to form the flecainide product in one step or with two 2-aminomethyl-pyridine followed by reduction to form the flecainide product in two steps.

Individual reaction steps in the above scheme are presented as being novel per se, as are some of the intermediate compounds formed.

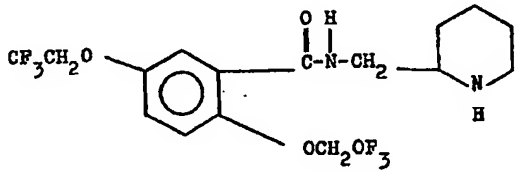
GB 2 045 760 A

SPECIFICATION

Process for the preparation of 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-piperidylmethyl) benzamide

This invention relates to an improved process for the preparation of the antiarryhythmic agent 2,5-bis(2,2,2-trifluoroethoxy)-B-(2-piperidylmethyl)benzamide (flecainide) and its salts from bromo- or hydroxy-substituted benzenes. The invention also relates to certain intermediate compounds produced in the process.

The antiarrhythmic compound, flecainide, its salts and a process for its preparation are described in United States Patent 3,900,481. Its structure is as follows

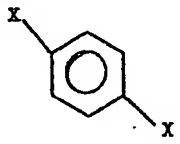


VIII

The present process is preferred to that of the prior art due to various practical advantages, e.g. the relatively low cost of the starting materials, the ease of carrying out the unit operations therein and the relatively high yields of the desired product.

Specifically, the process of the present invention comprises the following steps:

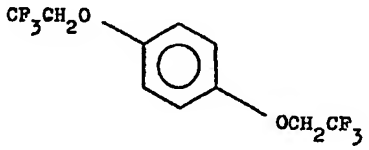
(1) reacting a compound of the formula



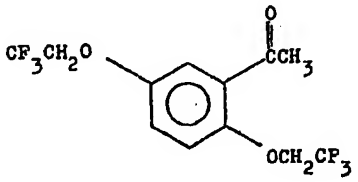
wherein the X's are the same and are selected from OH and Br with a suitable alkylating agent of the formula

CF_3CH_2O-A

wherein A is $-SO_2CF_3$ or an alkali metal to provide a compound of the formula

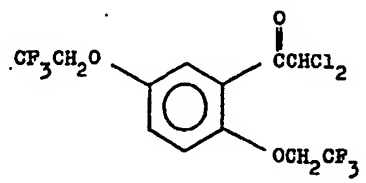


(2) acetylating in the presence of a Lewis acid catalyst to provide a substituted acetophenone of the formula



(3) then either

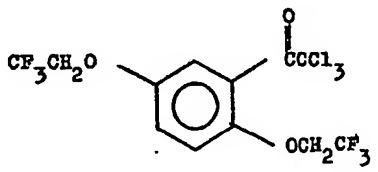
(a) chlorinating the substituted acetophenone (e.g. in acetic acid) to form the corresponding α,α-dichloroacetophenone



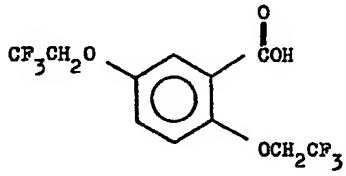
and

(b) adding a buffering base and further chlorinating to provide the α,α,α-trifluoroacetophenone

or

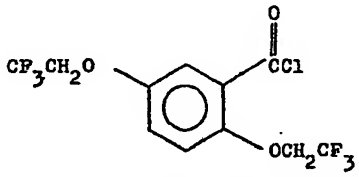


(c) reacting the substituted acetophenone with hypochlorite to form the corresponding benzoic acid



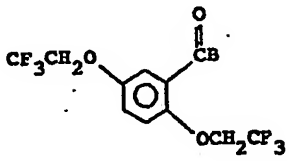
and

(d) reacting the acid with an inorganic acid chloride to provide the acid chloride



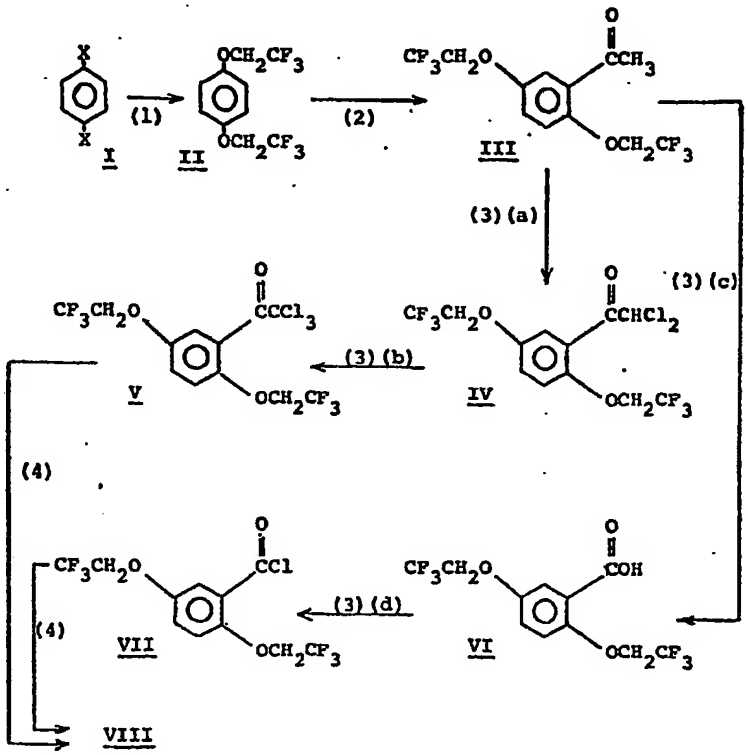
(4) and then reacting the product of step 3(b) or step 3(d) with 2-(aminomethyl)piperidine to form the desired product in one step, or with 2-(aminomethyl)pyridine and then reducing to form the desired product, option-as the free base.

The processes which comprise steps (1); (1) and (2); (3) (a); (3) (c); (1), (2) and (3) (c); (3) (b); (3) (a) and (3) (b); and (4) above constitute separate aspects of the overall invention as do the intermediate compounds



wherein B is selected from $-CH_3$, $-CHCl_2$ and CCl_3.

The overall process of the invention follows the reaction sequence:



In the first step of the process, X is OH, A is suitably $-SO_2CF_3$ and the reactants are heated together in a solvent such as acetone or N.N-dimethylformamide and in the presence of a base, preferably a weak base such as an alkali metal carbonate, e.g. potassium or sodium carbonate.

When X is BR, 1,4-dibromobenzene *I* is reacted with the 2,2,2-trifluoroethoxide ion in a strongly polar solvent mixture at a temperature up to the reflux temperature of the solution in the presence of cuprous or cupric ion to provide the desired product *II* in good yield. The 2,2,2-trifluoroethoxide ion is obtained from the corresponding alcohol by reaction with a strong base such as sodium hydroxide or preferably sodium hydride. Suitable solvent mixtures include dimethyl sulfoxide, N,N-dimethylacetamide and preferably N,N-dimethylformamide, each with about 10 to 50 percent, and preferably about 20 percent, of 2,2,2-trifluoroethanol. Cuprous ion is provided, e.g. by a cuprous halide such as cuprous iodide or cuprous bromide. Cupric ion is provided e.g. by cupric bromide, cupric sulfate or cupric acetate.

In step (2) the 1,4-bis(2,2,2-trifluoroethoxy)-benzene *II* produced in the first step is acetylated by reacting under mild conditions with any acetylating agent such as acetyl chloride or acetic anhydride in the presence of a Lewis acid catalyst such as tin chloride, ferric chloride or, preferably, aluminum chloride. The acetylation is carried out in a suitable non-reactive solvent such as a chlorinated hydrocarbon, such as dichloromethane, trichloroethylene or 1,2-dichloroethane, diethyl ether, tetrahydrofuran and the like. Unexpectedly, this reaction provides high yields of the desired acetophenone *III*.

The reaction of step (3) (a) is a simple chlorination of the intermediate *III* in a suitable solvent such as ethyl acetate, a chlorinated hydrocarbon or, preferably, in acetic acid solution. This reaction is carried out at a moderate temperature, preferably 50 to 60°C.

The product *IV* can be isolated if desired, or the chlorination carried on as in step (3) (b) to obtain the intermediate *V* by adding a buffering agent e.g. an acetate salt such as sodium acetate and raising the temperature slightly for example, to 80 to 100°C while continuing the chlorination.

The reaction of step (3) (c) is most conveniently carried out by adding the acetophenone *III* to a cold solution of an alkali metal or alkaline earth hydroxide (such as sodium hydroxide, potassium hydroxide or calcium hydroxide) which has been saturated with chlorine to pH 7 (forming the corresponding hypochlorite). The reaction is then facilitated by warming the reaction mixture. A very high yield of the desired 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid *VI* is obtained.

In step (3) (d) the acid is converted to the corresponding acyl chloride by reaction with an inorganic acid chloride such as thionyl chloride, phosphorous trichloride or phosphorous pentachloride (preferably phosphorous trichloride) at reflux with or without a suitable non-reactive solvent such as benzene or toluene or a halogenated hydrocarbon.

Step (4) of the process may be carried out directly from the saturated diamine 2-(aminomethyl)piperidine or indirectly from the unreduced diamine 2-(aminomethyl)pyridine. Thus, 2-aminomethylpiperidine can be reacted with the tri-chloroacetophenone product of step (3) (b) or the compound 2-aminomethylpyridine can

be reacted with the trichloroacetophenone product *V* of step (3) (b). In either case, the reaction proceeds readily without external heating in an inert solvent such as toluene, benzene, isopropyl alcohol, cyclohexane and the like. The reaction proceeds particularly readily and in high yield when the unreduced diamine is reacted in a mixture of toluene and cyclohexane.

When the final step of the process is carried out, starting with the acid chloride product *VII* of step (3) (d), it is also carried out directly from 2-(aminomethyl)piperidine or indirectly from 2-(aminomethyl)pyridine. The acid chloride product of step (3) (d) is reacted by heating in a non-reactive solvent such as glyme, benzene, toluene or diethyl ether (preferably glyme). Alternatively, 2-aminoethylpyridine can be reacted with the acid chloride product of step (3) (d) in the presence of a non-reactive solvent such as toluene or benzene. This mixture is heated at reflux in the presence of an acid acceptor (e.g. a tertiary amine such as triethylamine). The adduct obtained from the reactive of an 2-(aminomethyl)pyridine with either compound *V* or *VII* is reduced to the desired product *VIII* by catalytic hydrogenation in the presence of platinum oxide or (preferably) platinum on carbon. The solvent used for this reaction is methanol or a lower alkanoic acid such as (and preferably) glacial acetic acid and the preferred temperature range is 15 to 30°C. When acetic acid is used the product obtained is flecainide acetate.

The following examples illustrate the processes of the invention and the preparation of the intermediate products thereof, and are not intended to be limiting on the scope of the invention as described hereinabove.

EXAMPLE 1

Step (1) of the process: A = SO_2CF_3 and X = OH

To a mixture of 2.42 moles (334.4 g.) of potassium carbonate, 2.2 moles (510.6 g.) of 2,2,2-trifluoroethyl trifluoromethanesulfonate in 1.02 liters of acetone is added a solution of 1.0 mole (110 g.) of hydroquinone in 1.1. liters of acetone, slowly over a 2 hour period. The reaction is then heated at reflux for 24 hours, the reaction mixture is evaporated, and 2 liters of chloroform and 2 liters of water are added to the residue. The chloroform layer is separated, the aqueous layer is washed twice with 1 liter of chloroform, and the combined chloroform solution is washed with 1 liter of water. The chloroform solution is dried over magnesium sulfate, then concentrated under vacuum. Hexane is added to the residue and the solid product is collected by filtration and washed with hexane. Additional material is collected from the concentrated residues. A yield of 88 percent, 241 g. of 1,4-bis(2,2,2-trifluoroethoxy)benzene, m.p. 75-77°C. is obtained.

EXAMPLE 2

Step (1): A = Na and X = Br

To 0.20 mole (9.6 g.) of 50 percent sodium hydride in 40 ml. of N,N-dimethylformamide is added 40 ml. of 2,2,2-trifluoroethanol followed by 0.034 mole (8.0 g.) of 1,4-di-bromobenzene and 0.006 mole (1.0 g.) of cuprous iodide. The mixture is heated at its reflux temperature for 4 hours, then cooled to about 25°C. and filtered. The residue is washed with N,N-dimethylformamide. The solution is then poured into water, and the precipitate is separated by filtration. The product is dissolved in diethyl ether and filtered, and the filtrate solution is evaporated to provide a solid residue which is washed with hexane and dried. The product is 7.3 g. (80 percent) of 1,4-bis(2,2,2-trifluoroethoxy)benzene, m.p. 77 to 79°C.

The reaction is rerun as follows, varying the conditions and proportions of the constituents and utilizing cupric bromide as the catalyst: To a mixture of 4.8 g. of sodium hydride in 40 ml. of N,N-dimethylformamide is added 20 ml. (27.4 g.) of 2,2,2-trifluoroethanol. To this mixture is added 0.034 mole (8.0 g.) of 1,4-dibromobenzene and 1.0 g. of cupric bromide. The reaction mixture is heated at about 100°C. for two hours, then quenched with ice water. Acidification with hydrochloric acid and filtration produces 9.2 g. (99 percent) of white solid 1,4-bis(2,2,2-trifluoroethoxy)-benzene. The structure is confirmed by infrared spectral analysis.

EXAMPLE 3

Step (2) utilizing acetic anhydride as the acetylating agent

To a mixture of 2.43 moles (324 g.) of aluminum chloride in 648 ml. of dichloromethane is added a solution of 0.88 mole (274 g.) of 1,4-bis(2,2,2-trifluoroethoxy)benzene and 0.97 mole (92 ml.) of acetic anhydride in 880 ml. of dichloromethane over a 3 hour period while maintaining the temperature at above 0°C. The reaction mixture is then heated to its reflux temperature and stirred at reflux for 5 hours. The progress of the reaction is followed using thin-layer chromatography. The reaction mixture is placed in an ice bath and ice and 10 percent hydrochloric acid are added slowly to decompose the aluminum chloride complex. The temperature of the reaction mixture is not allowed to exceed 25°C. The organic phase is separated and washed once with 2 liters of 10 percent hydrochloric acid and then with 2 liters of water. The combined aqueous phase is extracted with several liters of dichloromethane. The organic phase is dried over magnesium sulfate, then evaporated to provide a moist residue. Hexane is added to the residue and the resulting solid is collected by filtration and washed with hexane. Upon drying, 250 g. of light yellow crystalline 2,5-bis(2,2,2-trifluoroethoxy)acetophenone is obtained. The yield is 90 percent, the m.p. is 84 to 86°C.

EXAMPLE 4

A scale up of the run of Example 3

To a mixture of 4,367 grams (32.75 moles) of aluminum chloride and 8.8 liters of dichloromethane at 0°C. is added gradually a solution of 3,267 grams of 1,4-bis-(2,2,2-trifluoroethoxy)benzene and 1.399 kilograms (13.7 moles) of acetic anhydride in 1.3 liters of dichloromethane. The reaction temperature is maintained at 5 to 10°C. while stirring the mixture for about 16 hours. The reaction mixture is then heated to its reflux temperature and maintained under reflux for 4 hours. The reaction mixture is then acidified with 8.76 kilograms of 10 percent hydrochloric acid. Ice is added to the mixture to maintain the temperature below 20°C. The organic layer is separated and the aqueous layers are extracted several times with dichloromethane. The organic layers are dried, then evaporated to provide a residue which is triturated with hexane to provide a yellow solid product. Two crops of product are obtained providing a total yield of 3.088 kilograms of 2,5-bis(2,2,2-trifluoroethoxy)acetophenone, m.p. 84 to 88°C., yield 82 percent.

EXAMPLE 5

Step (2) utilizing acetyl chloride as the acetylating agent

To a mixture of 0.022 mole (2.8 g.) of aluminum chloride and 100 ml. of 1,2-dichloroethane is added dropwise at 25°C. a solution of 0.020 mole (5.6 g.) of 1,4-bis(2,2,2-trifluoroethoxy)benzene and 0.022 mole (1.76 g.) of acetyl chloride in 20 ml. of 1,2-dichloroethane. After stirring for 4 hours the reaction mixture is washed with ice water and hydrochloric acid and the organic layer is dried. Evaporation produces a residue which is recrystallized from hexane to provide 4.1 g. (71 percent) of pale yellow needles of 2,5-bis(2,2,2-trifluoroethoxy)acetophenone (as verified by infra-red spectral analysis).

EXAMPLE 6

Step (3) (a)

A mixture of 0.25 mole (79.1 g.) of 2,5-bis(2,2,2-trifluoroethoxy)acetophenone in 150 ml. of acetic acid is heated to 50°C. Chlorine gas is bubbled into the solution and the temperature increases gradually to 55°C. The chlorine addition rate is adjusted to maintain the temperature between 55 and 60°C. After about 75 minutes the temperature begins to decrease (indicating that no more chlorination is taking place). The total amount of chlorine added is 35.5 g. The resulting product is 2,5-bis(2,2,2-trifluoroethoxy)-α,α-dichloroacetophenone.

EXAMPLE 7

Step (3) (b)

To the product of the preceding example (without isolation or purification) is added 0.35 mole (28.7 g.) of sodium acetate. The temperature increases to about 80°C., and the solution is heated to 85°C. Chlorine addition is resumed and the temperature increases to 100°C. After about 20 minutes the theoretical amount of chlorine has been taken up, and the mixture is poured onto a mixture of ice and water. The precipitate which forms is collected by filtration, rinsed with water, dissolved in dichloromethane and dried. Evaporation provides a residue which is triturated with hexane to provide a white solid. A yield of 94 g. (90 percent) of 2,5-bis(2,2,2-trifluoroethoxy(∝,α,α-trichloroacetophenone, m.p. 45 to 48°C. is obtained.

EXAMPLE 8

Step (3) (c)

To a solution of 7.3 moles (292 g.) of sodium hydroxide in 600 ml. of water is added ice to make the total volume of 1.75 liters. Chlorine gas is passed into the solution while maintaining the temperature below 10°C. until it is neutral to litmus, and 2.19 moles (87.6 g.) of sodium hydroxide dissolved in 200 ml. of water is added. The combined solution is warmed to 50°C., and 0.73 mole (230 g.) of 2,5-bis(2,2,2-trifluoroethoxy)acetophenone is added slowly. The reaction mixture is stirred while heating until an exotherm begins about 75°C. and is thereafter maintained at about 80°C. by cooling. The mixture is stirred for about 16 hours at about 80 to 90°C. while monitoring the extent of the reaction by thin-layer chromatography. The excess hypochlorite is then destroyed by adding 75 g. of sodium bisulfite in 250 ml. of water, and the mixture is cooled to about 25°C. and carefully acidified with 10 percent hydrochloric acid. The light yellow solid product is collected by filtration, washed with water, and dried. A 94.5 percent yield of 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid, m.p. 120-122°C. is obtained.

EXAMPLE 9

Step (3) (d)

To a solution of 0.688 mole (219 g.) of 2,5-bis-(2,2,2-trifluoroethoxy)benzoic acid in 657 ml. of benzene is added 1,376 M. (100 ml.) of thionyl chloride slowly over 1 hour while heating to about 60°C. The mixture is then heated at reflux for about 8 hours, then evaporated to provide the desired product, 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid chloride as a residue. The structure is verified by means of infrared spectral analysis.

EXAMPLE 10

Step (4) carried out in two reactions starting with intermediate V

To a solution of 0.05 mole (21.0 g.) of 2,5-bis-(2,2,2-trifluoroethoxy)-α,α,α-trichloroacetophenone in 60 ml. of toluene is added dropwise a solution of 0.055 mole (6.0 g.) of 2-aminoethylpyridine in 50 ml. of cyclohexane and 10 ml. of toluene. The reaction is exothermic, and a precipitate forms immediately. Additional toluene and cyclohexane are added to obtain a mixture consistency that permits stirring, and the stirring is continued for two hours at about 25°C. The solid is then separated by filtration, washed with a mixture of toluene and cyclohexane and dried to provide a white solid. The product is 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-pyridylmethyl)benzamide, m.p. 104-106°C., 17.8 g., 89 percent yield.

A mixture of 0.33 mole (134.7 g.) of 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-pyridylmethyl)benzamide, 1.347 liters of glacial acetic acid and 13.5 g. of 5 percent platinum on carbon is reduced in a Parr apparatus at about 30 pounds of hydrogen at room temperature. The reaction is complete in 6-7 hours. The reaction mixture is filtered and the catalyst is washed with isopropyl alcohol. The solution and washings are evaporated to provide a residue. Hexane is added to the residue and the resulting white solid is collected and recrystallized from a mixture of acetona and hexane. A 71 percent field of 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-piperidylmethyl)-benzamide acetate, m.p. 150 to 152°C., is obtained. By concentrating the residual liquid, an additional 18 percent of product is obtained as a second crop with a melting point of 148-150°C.

EXAMPLE 11

Step (4) carried out in a single reaction starting with intermediae V

To a solution of 0.01 mole (4.19 g.) of 2,5-bis-(2,2,2-trifluoroethoxy)-α,α,α-trichloroacetophenone in 50 ml. of isopropyl alcohol is added 0.01 mole (1.2 g.) of 2-amino-methylpiperidine. The mixture gradually turns solid over a period of 30 minutes. The mixture is allowed to sit for about 16 hours, then 0.01 M of acetic acid and 4 ml. of isopropyl alcohol are added, and the solution is warmed to dissolve all of the solid. On cooling, 3.0 g. of a white solid are obtained. The filtrate is evaporated, and the residue recrystallized from isopropyl alcohol to give additional product as a white solid. The product is 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-piperidylmethyl)benzamide acetate according to its infrared and nuclear magnetic resonance spectra.

EXAMPLE 12

Step (4) carried out in two reactions starting with intermediate VII

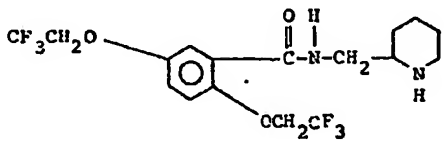
To a mixture of 0.77 mole (83.3 g.) of 2-aminomethylpyridine, 0.77 mole (106.7 ml.) of triethylamine and 300 ml. of benzene is added 0.70 mole (236 g.) of 2,5-bis(2,2,2-tri-fluoroethoxy)benzoic acid chloride in 472 ml. of benzene over 1 hour.

The reaction mixture is stirred for about 16 hours at 25°C., refluxed for one hour, then washed twice with 2 liters of water. The aqueous phase is washed with 2 liters of benzene, and the combined organic phases are dried over magnesium sulfate, then evaporated under vacuum. Recrystallization from a mixture of benzene and hexane give 240 g., 86 percent, of off-white 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-pyridylmethyl)benzamide, m.p. 100 to 102°C.

A mixture of 0.33 mole (134.7 g.) 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-pyridylmethyl)benzamide, 1.347 liter of glacial acetic acid and 13.5 g. of 5 percent platinum on carbon is reduced in a Parr apparatus at a pressure of about 10 pounds of hydrogen at room temperature. The reaction is complete in 6-7 hours. The reaction mixture is filtered and the catalyst is washed with isopropyl alcohol. The solution and washings are evaporated to provide a residue. Hexane is added to the residue and the resulting white solid is collected and recrystallized from a mixture of acetone and hexane. A 71 percent yield of 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-piperidylmethyl)benzamide acetate, m.p. 150 to 152°C., is obtained. By concentrating the residual liquid an additional 18 percent of product is obtained as a second crop with a melting point of 148-150°C.

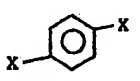
CLAIMS

1. A process for preparing a compound of the formula



which comprises

(1) reacting a compound of the formula

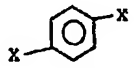


wherein the X's are the same and are selected from OH and Br with a suitable alkylating agent of the formula

CF_3CH_2O-A

wherein A is $-SO_2CF_3$ or an alkali metal to provide 1,4-bis(2,2,2-trifluoroethoxy)benzene,
(2) acetylating in the presence of a Lewis acid catalyst to provide 2,5-bis(2,2,2-trifluoroethoxy)acetophenone,
(3) then either
(a) chlorinating the substituted acetophenone to form 2,5-bis(2,2,2-trifluoroethoxy)-α,α-dichloroacetophenone, and
(b) adding a buffering base and further chlorinating to provide 2,5-bis(2,2,2-trifluoroethoxy)-α,α,α-trichloroacetophenone, or
(c) reacting the substituted acetophenone with hypochlorite to form 2,5-bis(2,2,2-trifluoroethoxy)benzoic acid, and
(d) reacting the acid with an inorganic acid chloride to provide the acid chloride,
(4) and then reacting the product of step (3) (b) or step (3) (d) with 2-(aminomethyl)-piperidine to form the desired product in one step, or with 2-(aminomethyl)pyridine and then reducing to form the desired product, optionally as the free base.

2. A process for preparing the compound 1,4-bis(2,2,2-trifluoroethoxy)benzene which comprises reacting a compound of the formula

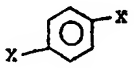


wherein all of the X's are the same and are selected from OH and Br with a suitable alkylating agent of the formula

$$CF_3CH_2O\text{-}A$$

wherein A is $-SO_2CF_3$ or an alkali metal.

3. A process for preparing the compound 2,5-bis(2,2,2-trifluoroethoxy)acetophenone which comprises
(1) reacting a compound of the formula



wherein the X's are the same and are selected from OH and Br with a suitable alkylating agent of the formula

$$CF_3CH_2O\text{-}A$$

wherein A is $-SO_2CF_3$ or an alkali metal to provide 1,4-bis(2,2,2-trifluoroethoxy)benzene, and
(2) acetylating in the presence of a Lewis acid catalyst.

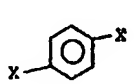
4. A process for preparing the compound 2,5-bis(2,2,2-trifluoroethoxy)-α,α-dichloroacetophenone which comprises chlorinating 2,5-bis(2,2,2-trifluoroethoxy)acetophenone.

5. A process for preparing 2,5-bis(2,2,2-trifluoroethoxy)-α,α,α-trichloroacetophenone which comprises adding a buffering base to 2,5-bis(2,2,2-trifluoroethoxy)-α,α-dichloro-acetophenone and chlorinating.

6. A process for preparing 2,5-bis(2,2,2-trifluoroethoxy)-α,α,α-trichloroacetophenone which comprises
(1) chlorinating 2,5-bis(2,2,2-trifluoroethoxy)acetophenone to form the corresponding α,α-dichloroacetophenone and
(2) adding a buffering base and further chlorinating to provide 2,5-bis(2,2,2-trifluoroethoxy)-α,α,α-trichloroacetophenone.

7. A process for preparing 2,5-bis(2,2,2-trifluoroethoxy)-benzoic acid which comprises reacting 2,5-bis(trifluoroethoxy)acetophenone with hypochlorite.

8. A process for preparing 2,5-bis(2,2,2-trifluoroethoxy)-benzoic acid which comprises
(1) reacting a compound of the formula



wherein both of the X's are the same and are selected from OH and Br with a suitable alkylating agent of the formula

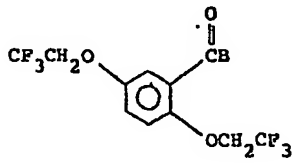
$$CF_3CH_2O\text{-}A$$

wherein A is $-SO_2CF_3$ or an alkali metal to provide 1,4-bis(2,2,2-trifluoroethoxy)benzene,
(2) acetylating in the presence of a Lewis acid catalyst to provide 2,5-bis(2,2,2-trifluoroethoxy)-acetophenone, and
(3) reacting the substituted acetophenone with hypochlorite to form the desired acid.

9. A process for preparing 2,5-bis(2,2,2-trifluoroethoxy)-N-(2-piperidylmethyl)benzamide which compris-

es reacting 2,5-bis(2,2,2-trifluoroethoxy)-α,α,α-trichloroacetophenone alternatively with 2-(aminoethyl)piperidine to form the desired product in one step or with 2-(aminoethyl)pyridine, then reducing to form the desired product, optionally as the free base.

10. A compound of the formula



wherein B is selected from $-CH_3$, $-CHCl_2$ and $-CCl_3$.

11. A process according to claim 1 wherein at least one of the steps (1) to (4) is substantially as hereinbefore described in an Example.

12. A process according to claim 2 wherein at least one of the steps is substantially as hereinbefore described in Example 1 or 2.

13. A process according to claim 3 wherein the alkylating step is substantially as hereinbefore described in Example 1 or 2 and/or the acetylating step is substantially as hereinbefore described in Example 3, 4 or 5.

14. A process according to claim 4 substantially as hereinbefore described in Example 6.

15. A process according to claim 5 substantially as hereinbefore described in Example 7.

16. A process according to claim 6 wherein the first chlorination is substantially as hereinbefore described in Example 6 and/or the second chlorination is substantially as hereinbefore described in Example 7.

17. A process according to claim 7 substantially as hereinbefore described in Example 8.

18. A process according to claim 8 wherein step (1) is substantially as hereinbefore described in Example 1 or 2 and/or step (2) is substantially as hereinbefore described in Example 3, 4 or 5 and/or step (3) substantially as hereinbefore described in Example 8.

19. A process according to claim 9 substantially as hereinbefore described in Example 10, 11 or 12.

20. A process according to claim 2 followed by reaction of the product according to claim 4 or 6.

21. A process comprising any one of steps 1,2,3a,3b and 4 of claim 1 or any consecutive combination of two or more thereof.

22. A process comprising any one of steps, 1,2,3c,3d and 4 of claim 1 or any consecutive combination of two or more thereof.

23. A process according to claim 21 or 22 substantially as hereinbefore described.

24. A process according to claim 21 or 22 substantially as hereinbefore described in an Example or Examples.

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